

Letters to the Editor**Sir Richard Doll on Chance and Genetic Susceptibility in Carcinogenesis, or, Why Not All Smokers Get Lung Cancer**

To the Editors: Your recent tribute (1) to Richard Doll ("the greatest epidemiologist of our time") brought to mind what must be one of the last articles he wrote. In it, he stressed the importance of chance in carcinogenesis and expressed his concern for what could be regarded as a one-sided genetic determinism in cancer research. I will let his words speak for themselves:

What I now find surprising, now that the concept of multiple mutations is so widely accepted, is that so many people fail to see that it accounts for the fact that only a relatively small proportion of people (<20%) are commonly victims of a particular type of cancer even if heavily exposed to known chemical carcinogenic agents. There have been two small groups of men who were very heavily exposed to chemical carcinogens in the course of their work in which all were affected, but they are atypical. The fact that only, say, 20% of heavy cigarette smokers would develop lung cancer by 75 years of age in the absence of other causes of death does not mean that 80% are genetically immune to the disease any more than the fact that usually only one cancer occurs in a given tissue implies that all the stem cells in the

tissue that have not given rise to a malignant clone are also genetically immune. What it does mean is that whether an exposed subject does or does not develop a cancer is largely a matter of luck: bad luck if the several necessary changes all occur in the same stem cell when there are several thousand such cells at risk, and good luck if they do not. Personally, I find that makes good sense, but many people apparently do not (2).

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References

1. Potter JD, Prentice R, Weiss N. Obituary: Richard Doll. *Cancer Epidemiol Biomarkers Prev* 2005;14:2825.
2. Doll R. Commentary: the age distribution of cancer and a multistage theory of carcinogenesis. *Int J Epidemiol* 2004;33:1183-4.

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